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Percutaneous Transcatheter Mitral Valve Replacement An Overview of Devices in Preclinical and Early Clinical Evaluation

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Mitral regurgitation (MR) is one of the most prevalent valvular heart diseases in Western countries. The current estimated prevalence of moderate and severe MR in the United States is 2 to 2.5 million, and it is expected that this number will rise to 5 million by 2030.¹ Surgical intervention is recommended for symptomatic severe MR or asymptomatic severe MR with left ventricular (LV) dysfunction.² Treatment of degenerative MR has evolved from mitral valve (MV) replacement to MV repair because of superior long-term outcomes after repair.²⁻⁴ For functional MR, however, the benefit over MV replacement is less certain.⁵ In addition, minimally invasive MV surgery has become a well-established and increasingly used option for managing patients with MV pathology.⁶

Although surgery remains the gold standard treatment for significant MR, MV surgery is deferred in a large number of patients because of high surgical risk.⁷ The decrease in the prevalence of rheumatic valve disease, in combination with an increased life expectancy, has led to a high prevalence of degenerative MR. As a consequence, patients are older and present with comorbidities that increase operative mortality and morbidity risks.⁸ In octogenarians, there has been reported a mortality and morbidity rate of 17.0% and 35.5%, respectively, following MV surgery.⁹ This results in denial or nonreferral for surgery in a large group of patients with significant MR—the Euro Heart Survey revealed that up to 50% of patients hospitalized with symptomatic severe MR are not referred for MV surgery, mainly because of advanced age, comorbidities, and LV dysfunction. In patients aged ≥80 years, surgical treatment was performed in only 15% compared to 60% in patients aged ≤70 years.^{8,10}

The observation that a significant number of patients are not referred for MV surgery and the desire for less invasive approaches have led to the development of different percutaneous approaches aiming at treating MR.

Transcatheter MV Repair

During the past few years, several percutaneous transcatheter MV repair (TMVR) technologies have emerged as possible

alternatives to open surgery for high-risk patients, and these technologies are currently at different stages of investigation and clinical implementation. A classification of percutaneous TMVR technologies on the basis of anatomic targets is proposed and groups the devices into those targeting the following: (1) leaflets: percutaneous leaflet plication (edge-to-edge MV repair), leaflet coaptation, leaflet ablation; (2) annulus: indirect annuloplasty through the coronary sinus or direct annuloplasty (true percutaneous or by hybrid approach); (3) chordae: percutaneous chordal implantation; or (4) LV: percutaneous LV remodeling.¹¹

The device with the largest clinical experience is the MitraClip system (Abbott Laboratories, IL) using the edge-to-edge clip technique for percutaneous MV repair. The EVEREST (Endovascular Valve Edge-to-Edge Repair Study) II study is the only randomized controlled trial with published data comparing MitraClip therapy with conventional surgery in degenerative MR. One-year results showed that percutaneous MV edge-to-edge repair was less effective than surgery in reducing MR but that it was associated with superior safety and similar improvements in clinical outcome.¹² At 4-year follow-up, patients treated with the MitraClip system were reported to require more frequently MV surgery to treat residual MR compared with the surgical group, although no differences were observed after 1-year follow-up. In addition, there were no differences in the prevalence of (moderate)-severe MR or mortality at 4-year follow-up.¹³ As a result, the MitraClip system obtained approval from the US Food and Drug Administration in 2013 for patients with significant symptomatic degenerative MR who are at prohibitive risk for MV surgery. Trials studying the role of the MitraClip system in patients with symptomatic functional MR are still ongoing.

The other percutaneous TMVR technologies using the concepts of annuloplasty, chordal implantation, and LV remodeling are still under development, and although safety rates have generally been equal or superior to conventional surgery, efficacy has been suboptimal.^{11,14} In the future, multiple percutaneous repair techniques may be used in combination to

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increase overall efficacy.¹¹ However, for many patients MV repair will not be possible, and MV replacement will be required. Further limitations of TMVR_c are unequal tension on left atrium or mitral annulus (coronary sinus at a distance from annulus) when using coronary sinus reshaping devices, as well as the possibility of iatrogenic mitral stenosis.¹¹

Transcatheter MV Replacement

Transcatheter valve replacement for the treatment of diseased heart valves in selected patients is of increasing importance, with promising results after transcatheter aortic valve replacement.^{15–17} The performance of transcatheter aortic valve replacement has rapidly increased in the past few years—the number of procedures in Europe more than tripled in recent years, from 4500 in 2009 to >18 000 in 2011 (>50% of these were performed in octogenarians).¹⁸ In accordance, transcatheter MV replacement (TMVR) may have the potential to become an alternative to treat severe MR in patients who are at high surgical risk because of its theoretical possibility to reduce MR to a similar extent as surgery while reducing procedural risks. Furthermore, TMVR could offer a wider applicability across patient and disease variations compared with TMVR_c and can be made into a rather simple and fast procedure.

The feasibility of this approach has been reported for TMVR with the SAPIEN XT valve (Edwards, CA) and Melody valve (Medtronic, MN) in dysfunctional mitral bioprostheses and annuloplasty rings. These percutaneous valve-in-valve and valve-in-ring implantations of transcatheter heart valves have shown excellent hemodynamic performance with low transvalvular gradient and perivalvular regurgitation.^{19–24} In February 2014, Edwards received CE Mark approval for transcatheter mitral valve-in-valve procedures using the SAPIEN XT valve. Furthermore, 3 recent case reports described successful TMVR using balloon-expandable transcatheter heart valves in patients with a severely calcified native MV stenosis, indicating that MV disease with a calcified annulus may be treated with TMVR in selected high-risk patients.^{25–27}

The data showing that MV disease is undertreated worldwide coupled with the large number of patients not eligible for TMVR_c has driven the field of percutaneous TMVR. However, many challenges need to be addressed in the design of a device that targets the most complex of the heart's 4 valves.^{28,29} These challenges for TMVR devices are discussed more extensively in Table 1. Ideally, TMV implants should restore unidirectional flow while minimizing the risks associated with

Table 1. Challenges for Percutaneous TMVR Devices

Valve position

To be deployed in the left AV position, making a truly percutaneous, transfemoral delivery a challenge—because of the requirement for transseptal (or transaortic retrograde) access to the LA or LV and the need for a multidimensional, highly curved catheter course (which is challenging with a large delivery system and limits the precision with which tension and traction are transmitted to the operating end of the system)

Possible access routes: transapical, transseptal, transatrial

Valve anatomy

Should fit an asymmetrical saddle-shaped mitral annulus

There is no stable calcified structure for anchoring (unlike for TAVR) in most cases*

The mitral valve is a complex structure composed of leaflets, annulus, chordae tendineae, and papillary muscles—preservation of the subvalvular apparatus is mandatory to preserve LV geometry

There is an irregular geometry of the mitral valve leaflets

Dynamic environment

There are dynamic changes in mitral annular geometry (shape/size) during the cardiac cycle, resulting in an overall reduction of annular area up to 30% and a reduction of annular circumference of up to 15%³⁰

The device should be resistant to displacement or migration while enduring continuous cyclic movements of the annulus and LV base, as well as high transvalvular gradients (high dislodgment forces)

Device requirements

The device should have a balanced radial stiffness to resist the dynamic environment and avoid frame fracture, whereas at the same time its stiffness should not cause perforation of adjacent structures.

Valve materials must be durable enough to withstand the loads generated

The device should not obstruct the left ventricular outflow tract, occlude the circumflex coronary artery, compress the coronary sinus, or cause major conduction system disruption

Because of the large annular size, there is a need for large delivery systems

Hemodynamic performance

Paravalvular leak (PVL) should be minimized because regurgitation is poorly tolerated in the mitral position as a result of the higher pressure gradient across the valve. Moreover, PVL may result in hemolysis.

The TMVR should restore unidirectional flow while minimizing the risks associated with the procedure

Other issues

Thrombogenicity of a bulky device implanted in the left AV position

Possibility of reoperation or TMVR-in-TMVR is still unclear

AV indicates atrioventricular; LA, left atrium; LV, left ventricle; TAVR, transcatheter aortic valve replacement; and TMVR, transcatheter mitral valve replacement.

*In some patients with mitral valve stenosis, it is possible to anchor the device in the severely calcified mitral annulus.^{25–27}

the procedure, allowing high-risk and inoperable patients to receive definitive treatment.

This review aims to give an overview of the different percutaneous TMVR technologies currently under development. We report a list that is complete to the best of our knowledge. All manufacturers were asked to provide information on valve design and (pre)clinical results—this information was integrated with data available in peer-reviewed journals as well as with information provided by the coauthors that was not published before. Many of the device specifications and image material are published here for the first time; still some information could not be provided because of confidentiality reasons.

CardiaQ Valve

Device

The CardiaQ valve (CardiaQ Valve Technologies, CA) consists of a self-expanding nitinol frame, which carries 3 leaflets of bovine pericardial tissue. The device is designed in such a way that it does not use radial force for fixation to the annulus. Two sets of anchors grasping the mitral leaflets from the left atrial and LV side are used for fixation of the valve prosthesis. In addition, foreshortening of the frame creates a clamping action that anchors the valve above and below the annulus. The chordae and papillary apparatus should normally be preserved (Figure 1A). The different steps of valve deployment should be well controllable, and the fact that the valve is designed to be repositionable before final deployment should help ensure accurate placement (Figure 1B–1F). The device can be inserted truly percutaneously through the femoral vein using a transseptal access to the left atrium (antegrade). Alternative access is a transapical approach (retrograde).

Preclinical Development

Preclinical assessment of safety and feasibility of the CardiaQ valve has been successful. Animal experiments were conducted in 20 swine. A correct implantation position was obtained in 14 of 19 animals, whereas an infra- and supra-annular implant was observed in 4 and 1 animal(s), respectively. One animal was lost before initiating the procedure. None of the valves migrated or embolized after implantation. Successful implantation resulted in an excellent TMV function and stable hemodynamics, with no LV outflow tract (LVOT) obstruction, coronary artery obstruction, or transvalvular gradient (unpublished data, presented at TCT 2012 by L. Søndergaard).

First-In-Human

A milestone was achieved on June 12, 2012, when the first-in-human TMVR was conducted at Rigshospitalet, Copenhagen, Denmark. The patient, a 86-year-old man experiencing symptomatic severe MR grade IV+, was declined for MV surgery and MitraClip treatment. With the use of an antegrade transseptal approach, a CardiaQ valve was successfully implanted, resulting in an accurate and stable position. The first 24 hours, the patient made an uneventful recovery and was hemodynamically stable. However, despite a well-functioning TMV prosthesis, the patient died 3 days postprocedure

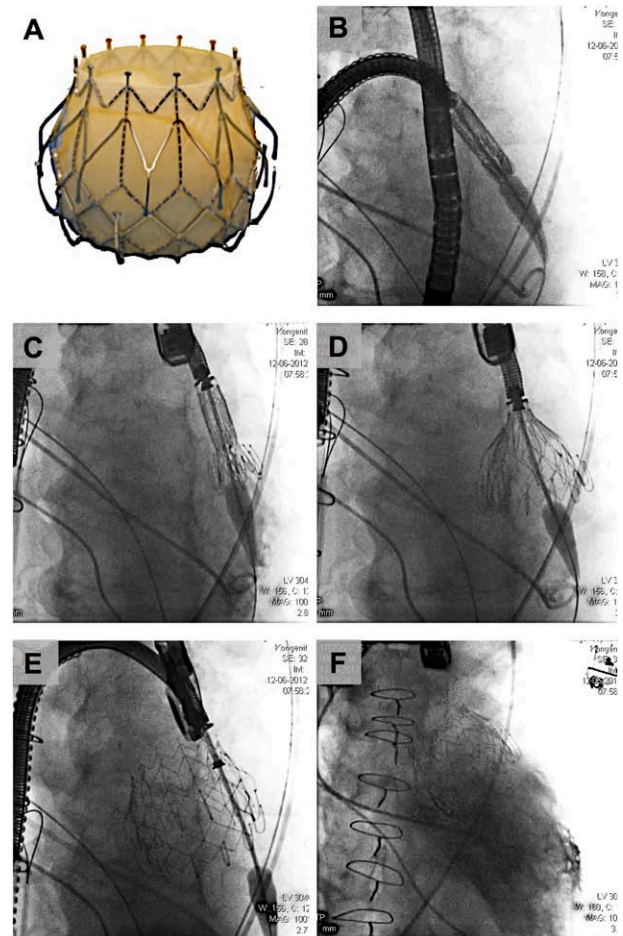


Figure 1. CardiaQ valve. **A**, The valve consists of a self-expanding nitinol frame that carries 3 leaflets of bovine pericardial tissue. Implantation sequence of CardiaQ valve: **(B)** coaxial alignment, **(C)** opening of the ventricular anchors, **(D)** opening of the atrial anchors, and **(E)** final release of the CardiaQ valve before removal of the delivery system. **F**, Left ventriculogram showing good position of the transcatheter mitral valve prosthesis and absence of significant mitral regurgitation. **A**, Image was provided by and is the property of CardiaQ Valve Technologies, Inc. Printed with permission. **B–F**, Images courtesy of Dr Søndergaard. Printed with permission.

because of multiorgan failure (unpublished data, provided by L. Søndergaard).

Tiara Valve

Device

The Tiara valve (Neovasc Inc, British Columbia, Canada) is a self-expanding bioprosthesis with cross-linked bovine pericardial tissue leaflets mounted inside a metal alloy frame. The atrial portion is designed specifically to fit the saddle-shaped mitral annulus; the D shape should match the natural shape of the mitral orifice and prevent impingement of the LVOT. The ventricular portion of the device comprises a covered skirt to prevent paravalvular leakage (PVL), as well as 3 anchoring structures. The 2 anterior anchoring structures are designed to capture the fibrous trigones at both sides of the anterior MV leaflet, whereas the posterior anchoring structure projects behind the posterior MV leaflet, thus creating a 3-point

anchor on the ventricular side that works in conjunction with the atrial flange to secure the prosthetic valve within the mitral annulus. This securement should prevent retrograde dislodgment during systole (Figure 2).^{28,31} In all stages, until the final step of ventricular deployment, the Tiara valve should be fully retrievable and repositionable. Implantation is performed transapically by means of a 32F delivery catheter and should not require rapid pacing (Figure 2).

Preclinical Development

Preclinical assessment of safety and feasibility of the Tiara valve has been successful.²⁸ This included both acute and chronic animal models, as well as human cadavers. In the acute animal model, Tiara valves were successfully

implanted in 29 of 36 (81%) swine. Implantation was unsuccessful in 7 animals because of improper positioning of the valve (n=3), failure of the valve anchors (n=2), and ventricular fibrillation (n=2). None of the valves migrated or embolized after implantation. There was a steady increase in the rate of successful implantation as the series progressed, with the final 12 animals all undergoing successful and uneventful implantation. Both acute and chronic evaluation demonstrated excellent valve function and alignment, with no LVOT obstruction, coronary artery obstruction, or transvalvular gradient. Chronic evaluation of 7 sheep demonstrated clinically stable animals throughout a follow-up of 150 days. The investigators attribute a relatively high rate of PVL observed in the chronic animal model to the fact that only one size of the Tiara valve was available, making size mismatch between the native

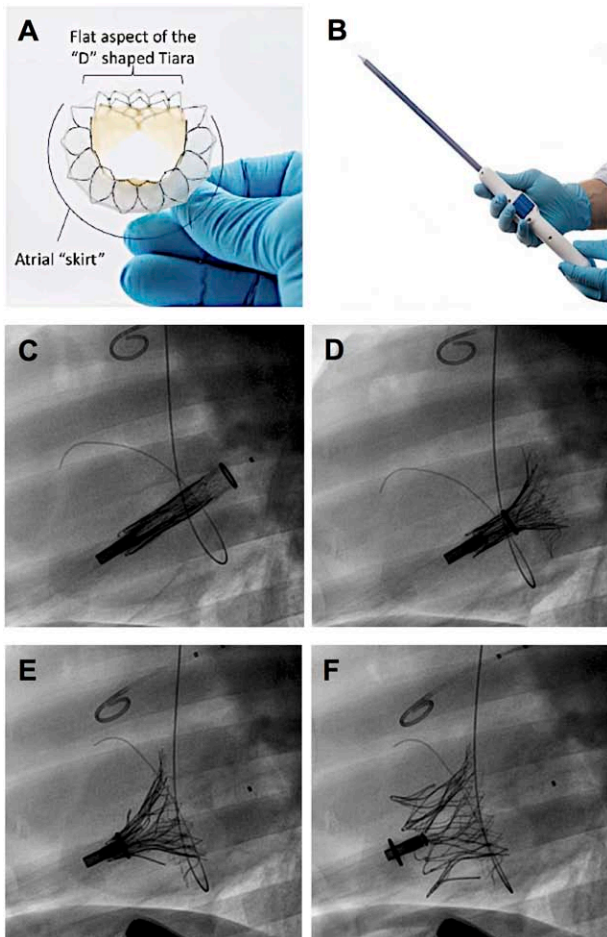


Figure 2. Tiara valve. **A**, The D-shape of the valve, the atrial skirt that engages the atrial aspect of the mitral annulus, and the saddle-shaped valve are clearly seen. **B**, Transapical 32F delivery system. Implantation sequence of Tiara valve: **(C)** the coronary sinus wire outlines the mitral annulus; the pigtail catheter is anteriorly in the ascending aorta, and the delivery system is through the mitral annulus into the left atrium; **(D)** opening of the atrial skirt in the left atrium and the flat aspect of the D-shaped Tiara are facing anteriorly; **(E)** the atrial skirt is open and positioned on the atrial aspect of the mitral annulus, and the ventricular portion of the Tiara valve is delivered into position just before final release; **(F)** final release of the Tiara valve, before removal of the delivery system. Reprinted from Banai et al²⁸ with permission of the publisher. Copyright ©2014, American College of Cardiology Foundation.

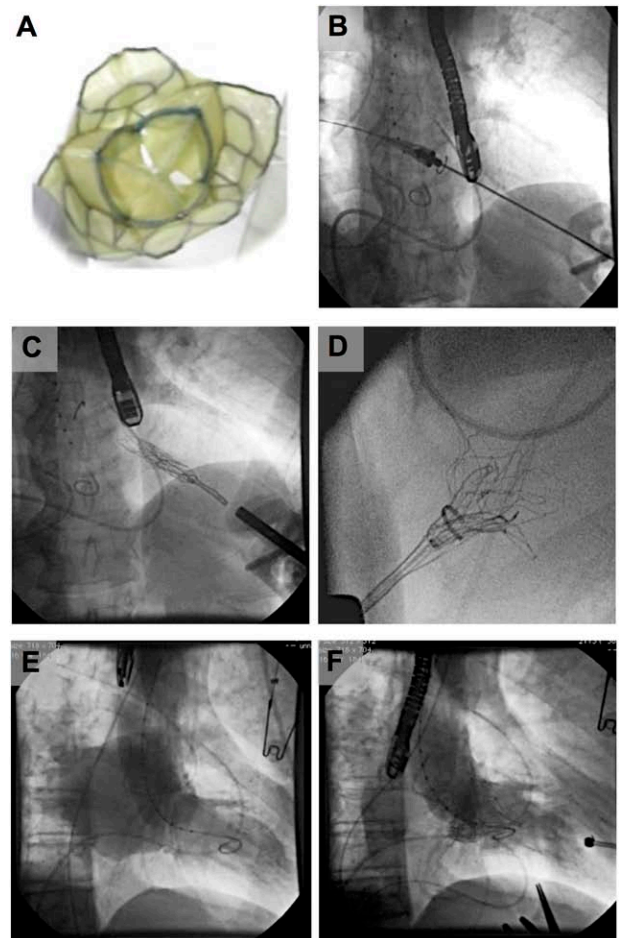


Figure 3. Tendyne valve. **A**, The valve consists of a self-expanding metal alloy frame made of an inner stent containing a trileaflet porcine pericardial valve and an outer stent that abuts the native mitral annular tissues. The device is secured in place using a polymer tether that passes through the left ventricle to an epicardial pad. Implantation sequence: **(B)** access of left atrium with dilator and sheath; **(C)** advancement of valve within sheath, deploying valve in left atrium; tether traction is used to position the valve in native annulus; **(D)** the polymer tether allows the valve to be captured for repositioning or replacement with alternative valve size, if necessary; **(E and F)** left ventriculogram showing elimination of severe mitral regurgitation in human subject. These images were provided by and are the property of Tendyne Inc. Printed with permission.

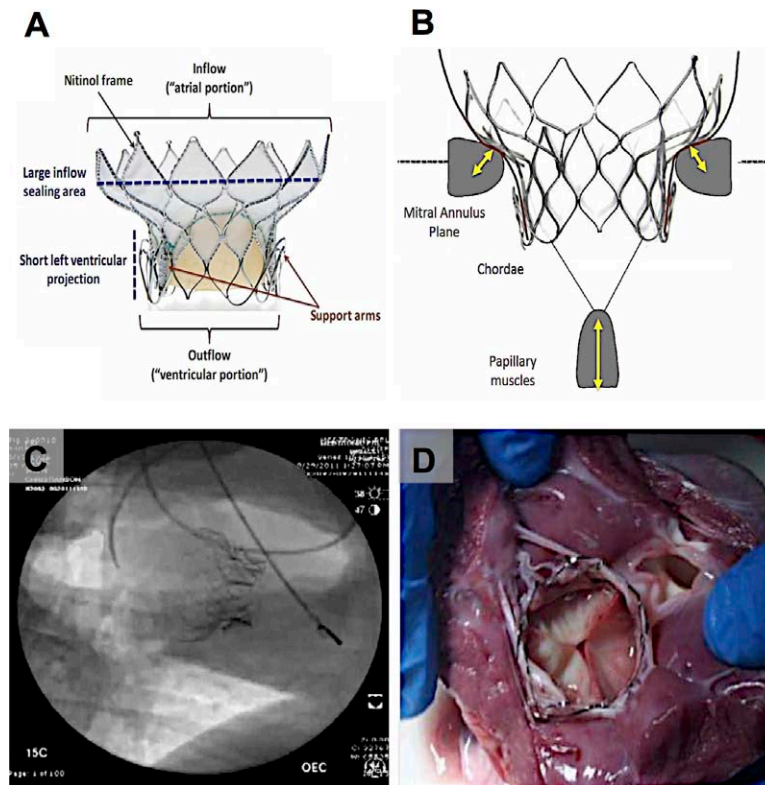


Figure 4. Medtronic transcatheter mitral valve. **A**, The bioprosthetic valve is a trileaflet pericardial valve—it has support arms that function to capture the anterior and posterior mitral valve leaflet and engage the submitral apparatus. **B**, The concept of axial fixation using the mitral apparatus to secure the device in position. **C**, Acute animal results showing good positioning with no central or paravalvular leak. **D**, Preservation of the submitral apparatus and no left ventricular outflow tract obstruction. Images courtesy of Dr Piazza. Printed with permission.

annulus and prosthetic device unavoidable in many hearts. In situ cardioscopy showed homogeneous coverage of the metal struts with a white fibrotic connective tissue layer, both along the atrial and ventricular struts. Macroscopic and microscopic evaluation demonstrated that devices seemed well seated, and all valve frames showed good incorporation by a thin pannus around the atrial and ventricular surfaces with fibrous tissue growth adequate for healing. The pericardial leaflets were intact without tears or perforations. The human cadaver model demonstrated that implantation resulted in appropriate geometric positioning with full circumferential coverage of the atrial aspect of the mitral annulus and good apposition and location of the ventricular anchoring system.²⁸

First-In-Human

The first 2 cases of human Tiara valve implantation were performed in January and February 2014 at St. Paul's Hospital, Vancouver, British Columbia, Canada. Both patients had severe functional MR, poor LV function, and were considered extremely high-risk candidates for conventional MV surgery. The transapical procedures resulted in immediate elimination of MR and improved LV stroke volumes, without the need for any cardiac support device and with no procedural complications (unpublished data, provided by manufacturer). The further outcome was kept confidential.

Tendyne Valve

Device

The Tendyne valve (Tendyne Inc, MN) is a trileaflet pericardial valve sewn onto a nitinol frame (Figure 3A). Because

the valve is a descendant of the Lutter valve, the Tendyne valve shares several design elements with the Lutter valve: (1) an atrial fixation system, (2) a ventricular body made of a nitinol self-expanding frame that accommodates a bioprosthetic heart valve, and (3) a ventricular fixation system composed of tethering strings attached to the stent. The Tendyne valve is designed to be fully retrievable, and precise deployment and accurate adjustment of its intra-annular position should be achievable to minimize the risk of PVL. The prosthetic valve is delivered transapically and is secured via a tether (neochordae) near the LV apex using a pad that sits on the epicardium.

Preclinical Development

The Lutter valve has been successfully implanted in several acute and chronic porcine models, with follow-up times of up to 2 months.^{32–39} During first studies, 30 pigs underwent off-pump mitral valved stent implantation with follow-up times of 60 minutes and 7 days. Accurate positioning was established in all but 5 animals. There were no issues of device migration, embolization, or LVOT obstruction. These studies proved the feasibility of reproducible deployment of the Lutter valve, achieving reliable prosthesis stability and adequate valve function in acute and short-term experimental settings. However, stent mal-deployment and fracture were 2 of the main complications seen throughout this study.³⁶

In a more recent study, adequate valve deployment and function were obtained in all but 1 animal with a newer prototype of the Lutter valve (n=6). Mild regurgitation developed after valve deployment in 1 animal just after 1 hour and in none thereafter. The average gradients across the valve

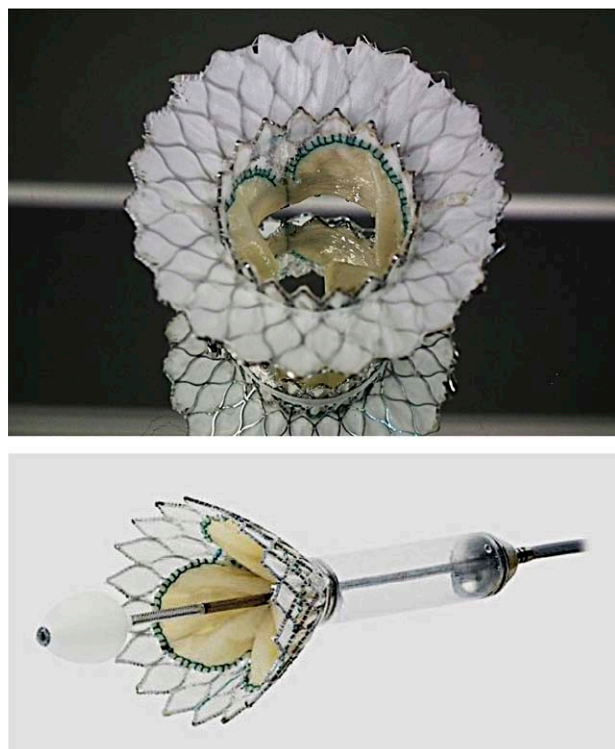


Figure 5. Valtech's Cardiovalve is a transcatheter mitral valve replacement system designed to be implanted using the transfemoral route. The implantation procedure is a 2-step approach: the first step involves implanting a sealing polyester skirt, and the second step is the implantation of the valve. These images were provided by and are the property of Valtech Cardio Ltd. Printed with permission.

and LVOT were low. All animals exhibited normal hemodynamics, and stability was maintained during follow-up. Migration, embolization, and PVL were not evident in the

remaining animals after 4 and 8 weeks. Gross evaluation revealed that 50% to 70% of the atrial element was covered by tissue growth at 4 to 8 weeks.³⁷

An additional study focused on the evaluation of 2 different frame designs: (1) the first design consisted of a circular crown-shaped atrial element connected to a tube-shaped ventricular element, and (2) in the second design, this atrial element was D-shaped to achieve better anatomic alignment. Although in vitro testing showed less PVL in the anteromedial region in D-shaped design stents, animal tests showed less favorable results, with rotational reorientation of all stents with D-shaped elements causing more severe PVL and preventing these advantages to take effect. Clearly, more studies are warranted to clarify this issue.^{38,39}

First-In-Human

The first 2 cases of human Tendyne valve implantation were performed in patients going to surgical MV replacement at the French Hospital, Asuncion, Paraguay (2013). The transapical procedure resulted in elimination of MR grade IV in one patient and reduction of MR grade IV to grade I in the other patient (unpublished data, provided by manufacturer). The further outcome was kept confidential.

Medtronic—TMV

Device

Medtronic's TMV is a trileaflet pericardial valve, optimized for the mitral position. The bioprosthetic valve features a large inflow atrial portion that is responsible for sealing and a short outflow ventricular portion to avoid LVOT obstruction. It has support arms that function to capture the anterior MV leaflet/

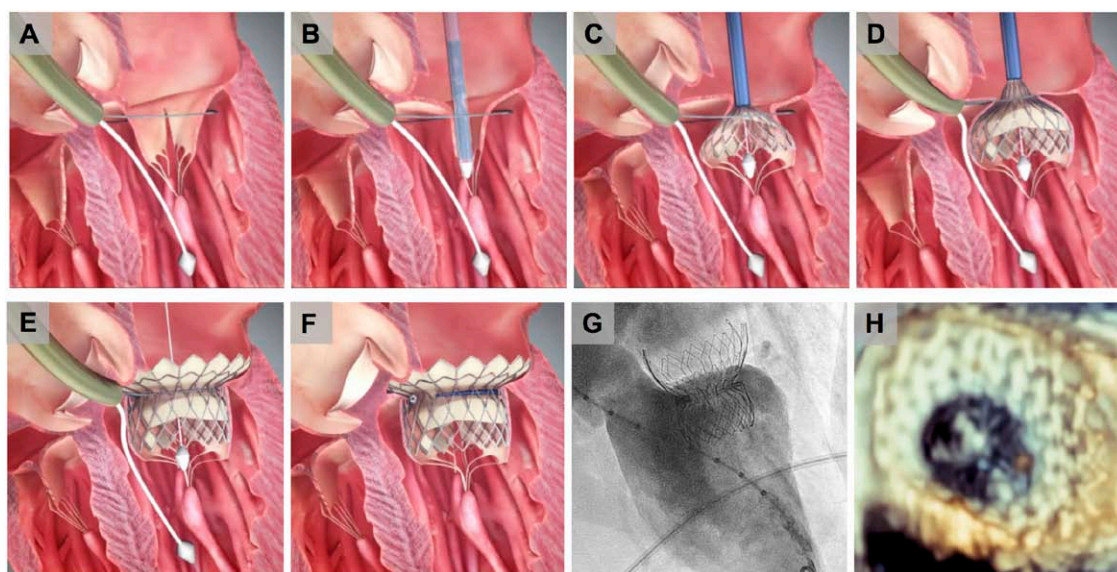


Figure 6. HighLife transcatheter mitral valve replacement system. The implantation procedure is a 2-step approach: **A** and **B**, The first step encompasses the placement of a locking component in the subannular space, using a transfemoral (transaortic) route; **(C–F)** the second step is the implantation of the HighLife valve over a transatrial access—on deployment of the stent-valve, the locking component automatically contacts the preformed groove in the stent-valve, creating a reliable anchoring and sealing mechanism in the annular region. **G**, Left ventriculogram showing good position of the HighLife valve and absence of mitral regurgitation. **H**, Transesophageal echocardiography (3D) image showing the trileaflet transcatheter mitral valve bioprosthesis during systole. These images were provided by and are the property of HighLife Medical. Printed with permission.

posterior MV leaflet and engage the submitral apparatus. The device is designed in such way that it should not rely on outward radial forces for anchoring; instead, it uses the mitral apparatus for axial fixation (Figure 4). The valve is designed to be fully retrievable and it should be possible to refold and withdraw the valve via a catheter in case a bailout procedure is needed. The current device is delivered transatrially, similar to a minimally invasive MV repair, with transseptal delivery under development.

Preclinical Development

In acute animal studies, Medtronic's TMV has been successfully implanted, resulting in accurate and stable valve positioning. Implantations were performed using a combination of fluoroscopic and echocardiographic guidance, combined with some tactile feedback when pulling on the catheter to engage the support arms under the A2-P2 leaflet segments. There was absence of central and paravalvular leakage, LVOT obstruction, and transvalvular gradients (unpublished data, presented at EuroPCR 2013 by N. Piazza).

FORTIS Valve

Device

The FORTIS TMV (Edwards Lifesciences Corp, CA) is composed of bovine pericardial tissue, a cloth-covered self-expanding frame designed to minimize PVL, and an anchoring system. The implantation is performed transapically.

First-In-Human

Edwards Lifesciences Corp announced on March 6, 2014, in a press release the successful completion of the first-in-human implants of its FORTIS transcatheter heart valve at St. Thomas' Hospital, London, UK (2014). The TMV was implanted transapically to treat 3 patients with severe MV disease and many risk factors that prevented them from undergoing surgery (unpublished data, provided by manufacturer). More detailed information is currently not available.

Cardiovalve

The Cardiovalve (Valtech Cardio Ltd, Or Yehuda, Israel) is a TMV prosthesis, designed to achieve fixation without radial force on the mitral annulus, yet obtaining full sealing and

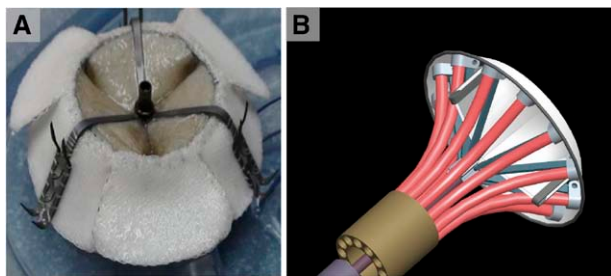


Figure 7. The EndoValve system is a foldable nitinol structure that is designed to conform to the mitral annulus and attaches to the native valve with specially designed grippers. The original EndoValve system is being redesigned to take advantage of MID's Permaseal technology to facilitate a transapical approach. Images courtesy of Dr Herrmann. Printed with permission.

freedom from LVOT obstruction. The device is intended to be implanted using the transfemoral route. The implantation procedure is a 2-step approach: the first step involves implanting a sealing polyester skirt, and the second step is the implantation of the valve (Figure 5). This 2-step approach should simplify the procedure and minimize the delivery system profile to 26F, thereby enabling transseptal crossing (unpublished data, provided by manufacturer). More detailed information is currently not available.

HighLife Medical—TMV

Device

HighLife Medical (CA) is developing a TMVR system based on the interaction of 2 components. Using a transfemoral approach, a locking component should be inserted in the LV and placed around the native mitral leaflets close to the annulus. Next, a stent valve should be deployed between the leaflets over a transatrial access. A dedicated groove in the stent-valve shape should automatically engage with the locking component and, in this way, create a consistent anchoring and sealing in the annular region (Figure 6).

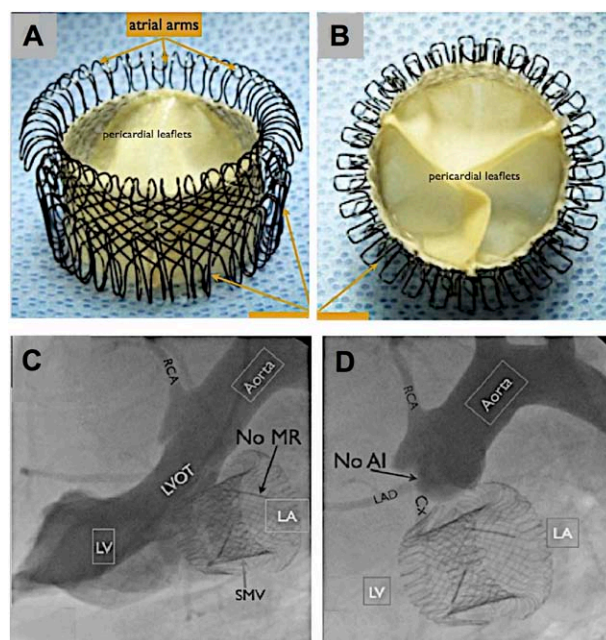


Figure 8. The Gorman device. **A** and **B**, This sutureless mitral valve replacement device consists of a frame constructed from a single nitinol wire that is woven into a complex 3-dimensional geometry engineered to provide a housing for the valve mechanism and anchoring forces to ensure secure position within the mitral annulus: **(A)** the device as seen from the side; **(B)** the device as seen from the ventricular side. The valve leaflets are constructed from porcine pericardium. **C** and **D**, Angiographic assessment of the Gorman device showing **(C)** the transcatheter mitral valve device is securely anchored and well functioning, without mitral regurgitation (MR) or left ventricular outflow tract (LVOT) obstruction, and **(D)** no aortic valve insufficiency. Cx indicates circumflex coronary artery; LA, left atrium; LAD, left anterior descending artery; LV, left ventricle; RCA, right coronary artery; and SMV, sutureless mitral valve. Reprinted from Gillespie et al⁴⁰ with permission of the publisher. Copyright © 2013, The Society of Thoracic Surgeons.

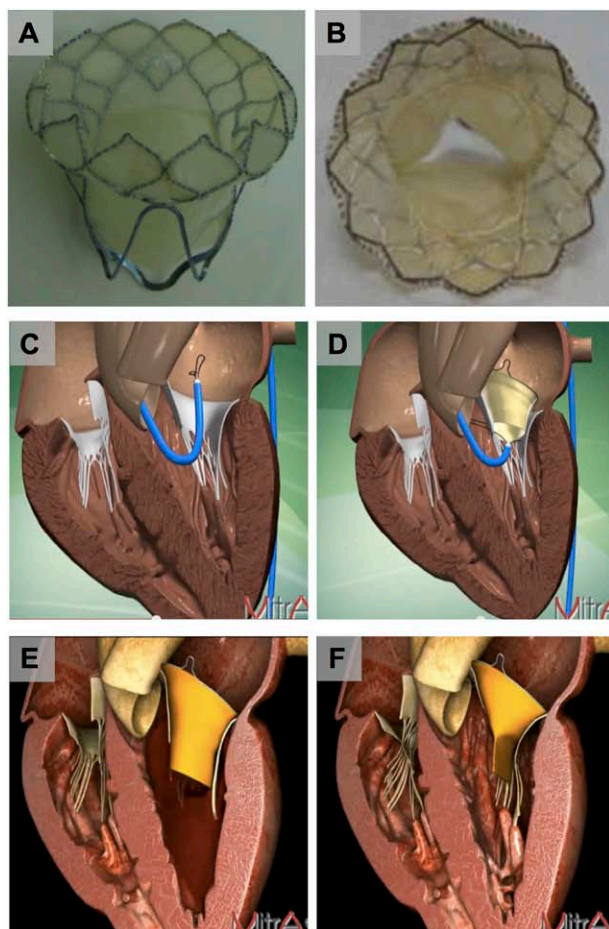


Figure 9. MitralAssist's valve-in-valve: a valve that assists the existing valve. **A** and **B**, The MitralAssist device consists of a nitinol frame with pericardium tissue and an asymmetrical bileaflet design. **C** and **D**, The device can be delivered through a low profile catheter (18Fr) via a transfemoral, transaortic route. **E** and **F**, The MitralAssist device should be suitable for almost all types of mitral regurgitation and has a low risk of left ventricular outflow tract obstruction. According to MitralAssist Medical, >90% of closure distance is promoted by the native leaflets and >80% of LV pressure is acting on the native valve apparatus. These images were provided by and are the property of MitralAssist Medical Ltd. Printed with permission.

Preclinical Development

Acute animal studies were reported to have shown adequate valve function and reproducibility (unpublished data, provided

by manufacturer). More detailed information is currently not available.

Endovalve

Device

Micro Interventional Devices (MID; Newtown, PA) acquired Endovalve, Inc—a spin-off from the University of Pennsylvania developing a TMV device based on patented technology from Dr Herrmann—in 2011. The Endovalve system was one of the earliest conceived designs, intended to improve on the limited efficacy of percutaneous repair technologies available in 2002. It is a foldable nitinol structure designed to conform to the anatomy of the mitral annulus and attach to the native valve with specially designed grippers (Figure 7). Although more detailed product specifications are not provided, MID reports that the Endovalve system is intended to be valve-sparing (subvalvular apparatus) and should provide a leak-proof MV replacement with no risk of LVOT obstruction.¹¹

The original Endovalve system is being redesigned to take advantage of MID's Permaseal technology to facilitate a transapical approach. The Permaseal system is a novel transapical access and closure device that combines soft-tissue anchors with advanced biocompatible elastomers to provide spontaneous (sutureless) wound closure after structural heart repair procedures.

Preclinical Development

Acute animal experiments were reported to be successful. A prototype of the Endovalve system functioned successfully for >30 minutes after implantation in 4 sheep (unpublished data, provided by manufacturer).

Gorman—TMV

Device

The TMV device designed by Gorman Cardiovascular Research Group (University of Pennsylvania, PA) is composed of a custom-designed nitinol framework and a pericardial leaflet valve mechanism (Figure 8). The frame is constructed from a single nitinol wire woven into a complex 3D-shape: the flexibility of this nitinol wire-weave stent body design should allow the device to gently conform to the complex MV geometry, creating a perivalvular seal without impingement on the

Table 2. Overview of the Different TMVR Devices

	Nitinol Frame	Trileaflet	Approach	Delivery System	Acute Animal	Chronic Animal	First-In-Human
CardiAQ	+	+	T-fem/T-ap	32F	+	+	+
Tiara	+	+	T-ap	32F	+	+	+
Tendyne	+	+	T-ap	30F	+	+	+
Medtronic	+	+	T-atr	NA	+	+	—
FORTIS	+	+	T-ap	NA	NA	NA	+
Cardiovalve	+	+	T-fem	26F	+	—	—
HighLife	+	+	T-atr	NA	+	—	—
Endovalve	+	+	T-ap	NA	+	—	—
Gorman	+	+	T-atr	30F	+	—	—
MitralAssist	+	—	T-ao	18F	+	+	—

NA indicates not available; T-ao, transaortic; T-ap, transapical; T-atr, transarterial; T-fem, transfemoral; and TMVR, transcatheter mitral valve replacement.

LVOT. The TMV device does not solely rely on radial force for anchoring strength. Anchoring is facilitated by a combination of gentle radial expansion and grasping arms that emanate from the ventricular aspect of the stent; these arms have been designed to insinuate themselves around the leaflets and chordae when the device is exposed to systolic LV pressures.⁴⁰

Preclinical Development

In acute animal studies, animals underwent on-pump TMVR using a left thoracotomy/atriotomy and a 30F delivery system. Echocardiographic, angiographic, and hemodynamic evaluation revealed normal LV systolic function and no significant PVL, LVOT obstruction, or MV stenosis. Necropsy demonstrated that the TMV devices were anchored securely. Finally, Gillespie et al⁴⁰ reported the intention to implant this device by means of an off-pump, minimally invasive thoracotomy or even a truly percutaneous transvenous, transseptal antegrade approach in the future.

MitrAssist

Device

MitrAssist Medical Ltd (Misgav, Israel) has developed an approach for the treatment of MR that is neither repair nor replacement. Instead, its valve implant is placed on top of the native MV with the intention to work in unison with it and to enhance valve functionality. The MitrAssist device consists of a nitinol frame with pericardium tissue and an asymmetrical bileaflet design (Figure 9). The MitrAssist device is designed to conform to the native MV's anatomic shape, preserve the natural MV functionality, and should have a low risk of migration or LVOT obstruction. The device should be repositionable before implantation and can be delivered through an 18F catheter.

Preclinical Development

Preclinical studies have been successfully completed in both in vitro/ex vivo beating heart and animal experiments. The MitrAssist device restored valve functionality in ex vivo beating heart experiments in which the native MV was severely damaged. A similar restoration of valve functionality was seen in short-term animal experiments, in which severe MR was successfully treated after MitrAssist implantation. In chronic animal studies, the device was reported not to jeopardize native MV functioning or create hemodynamic disturbances at 35 days postimplant, neither was there any report of leaflet trauma, adhesion, or thrombus formation (unpublished data, provided by manufacturer).

Conclusions

Percutaneous TMVR has proved to be feasible as valve-in-valve and valve-in-ring procedure in patients at high surgical risk. Results of animal experiments for TMVR in native MV have been encouraging and led the way to first-in-human implants, as accomplished with 4 different types of TMV devices. Many of the companies report that additional animal studies are ongoing or that first or additional human implants are anticipated within the current year (Table 2). However, multiple technical challenges are still to overcome before TMVR for native MR will become an option in daily practice. Nevertheless, with ongoing technological advancements in the field

of transcatheter valve replacement, it may be expected that TMVR may become a valuable alternative to MV surgery for patients with severe MR and a high surgical risk in the future.

Disclosures

Dr Piazza is a consultant for CardiAQ, Medtronic, and HighLife Medical. Dr Banai is Medical Director of Neovasc Inc. Dr Lutter is a consultant for Tendyne Inc. Dr Maisano is Chief Medical Officer and stockholder of Valtech Cardio and holds, or has applied for, patents related to the company. Dr Herrmann is a consultant for and has equity in Micro Interventional Devices. Dr Søndergaard is a consultant for CardiAQ. The other authors report no conflicts.

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KEY WORDS: catheters ■ mitral valve insufficiency

Percutaneous Transcatheter Mitral Valve Replacement: An Overview of Devices in Preclinical and Early Clinical Evaluation

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